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## Re: 'Long-term Results of a Randomized Controlled Trial Analyzing the Role of Systematic Pre-operative Coronary Angiography before Elective Carotid Endarterectomy in Patients with Asymptomatic Coronary Artery Disease'

We read with great interest the results of the study by Illuminati et al. regarding the predictive role of pre-operative coronary angiography before carotid endarterectomy (CEA) in patients with asymptomatic coronary artery disease (CAD).[1] These results also concur with their previously published results regarding early post-operative outcomes.[2] However, there are some interesting points that should be commented on.

Firstly, the group of patients who had not undergone a percutaneous coronary intervention (PCI) pre-operatively underwent CEA under single antiplatelet protection (aspirin), while the rest of the patients underwent CEA under dual antiplatelet protection (aspirin and clopidogrel) after undergoing PCI. Additionally, the first group showed a much higher incidence of myocardial infarctions (MIs) after CEA compared with the second group. But was this the effect of PCI itself or the effect of dual antiplatelet coverage? Have the authors considered that this could interfere with their results or produce potential bias? According to recent data, dual antiplatelet treatment reduces adverse cardiovascular outcomes after PCI by almost 20% compared with aspirin alone,[3] and also leads to a reduction of stent thrombosis after PCI.[4]

Secondly, the authors report that one MI was observed after a PCI re-stenosis. However, in the "Results" section, among all complications of PCI, the re-stenosis rate is not included in the secondary outcomes. In our view, it would be essential that the number of all asymptomatic re-stenoses after PCI that occurred during the study period should be reported. The presence of carotid artery disease alone has been associated with an increased risk for re-stenosis after PCI, justifying the reporting of such results.[5] Finally, re-stenosis remains an important adverse outcome after coronary angioplasty or stenting that may lead to cardiac complications or even necessitate a re-intervention.

Finally, regarding adverse cardiac events, another important issue is the designation of post-operative monitoring in patients undergoing CEA. In this trial, the authors state that they monitored patients during the first day after PCI, utilizing troponin measurements and electrocardiography (ECG) evaluation. But what exactly happened after CEA? Nine MIs were reported within 1 month of CEA in patients without pre-operative coronary angiography, although the exact monitoring protocol or the distribution of these events in the first days post-operatively is missing. Is this not essential for designing proper post-operative management? Recently, we have investigated the incidence of myocardial ischemia after CEA in different cardiac risk patients. In our cohort of 324 patients undergoing CEA, 44 presented with asymptomatic myocardial ischemia on the first and third post-operative days, independently from cardiac risk, and this was also associated with late cardiac events.[6] Previously, we have also estimated that the incidence of cardiac damage on the third day post-operatively reached almost 10% of the total of cardiac events post-CEA.[7] Therefore, a standardized monitoring of patients after CEA, including serum biomarker measurement and ECG evaluation, until at least the third post-operative day would, perhaps, be of more benefit.

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## Re: 'Long-term Results of a Randomized Controlled Trial Analyzing the Role of Systematic Pre-operative Coronary Angiography before Elective Carotid Endarterectomy in Patients with Asymptomatic Coronary Artery Disease'

We wish to thank Dr. Galyfos and his associates for their interesting and helpful comments. The fact that patients undergoing systematic coronary angiography/percutaneous coronary intervention (PCI) were treated on a dual antiplatelet regimen, whereas patients not undergoing coronary angiography were treated under a single antiplatelet regimen, was clearly mentioned in both of our papers as a potential source of bias.[1,2] Nonetheless, even taking into account the hypothesis that, according to Dr. Galyfos's own references,[3] a dual antiplatelet regimen could have reduced the incidence of post-operative myocardial infarction (MI). This would have resulted in, at most, a 20% relative reduction in the MI rate, therefore from 9% to 7% in the control group vs. none in the PCI group, which would still represent a significant difference in favor of prophylactic coronary revascularization. Furthermore, at discharge from the hospital, all patients in both study groups received a dual antiplatelet regimen and our most updated results have shown that pre-operative coronary angiography/PCI was correlated with a significant reduction in late MI. The hypothesis of a bias related to different medical regimens is therefore inconsistent. The rate of restenosis after PCI was not included among the secondary endpoints of the study because to schedule a coronary angiogram at regular time intervals in the absence of clinical symptoms of myocardial ischemia with a standard, normal cardiac work up, and with normal physical activity did not appear justified. Only one case of symptomatic re-stenosis of a previous PCI was observed during the entire study period, and this event did not affect the significant differences between the two study groups in terms of primary outcome. We obviously cannot rule out the possibility that a few, asymptomatic PCI restenoses might have occurred, but they did not translate into clinically evident MIs.

Finally, Dr. Galyfos and his associates suggest that limiting our cardiac monitoring to electrical changes and serum troponin level to the first post-operative day may have led us to miss out on some asymptomatic MI occurring beyond that period. However, since all the patients received strict cardiac follow up throughout the study, it seems highly unlikely that such events would not have translated into late ECG changes. Nonetheless, even assuming that this was the case, and according to Dr. Galyfos's own studies showing that asymptomatic post-operative myocardial ischemia is associated with late myocardial events independently from cardiac risk,[4,5] we can reasonably conclude that these asymptomatic and undetected post-operative myocardial ischemic events would be evenly distributed between the two groups, without modifying the statistically significant higher prevalence of MI in the non-coronary angiography group.

In any event, this type of speculation has little or no effect on the main results of our study, in which it has been shown that systematic pre-operative angiography followed by PCI or coronary artery bypass grafting, when needed, significantly reduces the incidence of post-operative and late MI, with fewer cardiac deaths and better late survival for our patients.

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